Clinical Ecology

Council on Scientific Affairs, American Medical Association

PHYSICIANS who practice clinical ecology believe that exposure to low levels of environmental substances present in the air or ingested from food and liquids causes in susceptible individuals a variety of ill-defined symptoms affecting nearly every organ system.

MULTIPLE CHEMICAL SENSITIVITY SYNDROME

Most physicians who practice clinical ecology (clinical ecologists) maintain that a number of patients have the multiple chemical sensitivity syndrome (MCSS) (also called clinical ecological illness, environmental illness, chemical AIDS facquired immunodeficiency syndrome], 20th-century disease, environmental hypersensitivity disease, total allergy syndrome, and cerebral allergy). 1-10 Clinical ecology has been defined as the orientation in medicine in which physicians primarily work with patients to uncover the cause-and-effect relationship between their ill health and food or lowlevel chemical exposure.9 Other definitions have been offered and no general agreement exists that clinical ecology and MCSS are synonymous.8-10 The lack of a clear definition or diagnostic test for MCSS has made it difficult to estimate its prevalence in the United States.

Clinical ecologists report that significant numbers of people have immune system derangements that increase their sensitivity to low levels of substances in the environment that are innocuous to normal people and are either inhaled (eg, the outside air, the workplace, or home) or ingested as liquids, foods, or drugs.4-6 Exposure to such substances in susceptible individuals is alleged to produce a polysymptomatic disorder that may involve any organ or many organ systems. Predisposing risk factors are said to include infection due to Candida albicans, a deficient or inadequate diet, and/or food intolerance. The primary complaints of such patients include allergy-like symptoms, food and chemical intolerance, rhinitis, difficulty in breathing, depression, headache, fatigue, irritability, insomnia, palpitations, and oth-

er cardiovascular symptoms.

A subset of MCSS is the Candida hypersensitivity syndrome.7 Some patients fit the criteria for chronic fatigue syndrome (CFS).11 Multiple chemical sensitivity is also claimed to be a cause or a contributing factor in the development of a number of recognized diseases and disorders (eg, migraine, various psychiatric illnesses, urticaria, anaphylaxis, atopic dermatitis, allergic rhinitis, asthma, learning disabilities, arthritis, and susceptibility to cancer).

Clinical ecologists propose a series of events to explain the development of MCSS. Low concentrations of a number of different chemicals over time are purported to damage the immune system and produce symptoms and sensitivity to other substances. The total load (body burden) of environmental insult is considered critical for the induction of illness. The concept of total load was introduced to explain inconsistent development of symptoms and variable doseresponse findings after experimental exposure to chemicals and food.3,12,13 Changes in the frequency of exposure and intervals between exposures to a specific antigen may delay the onset of symptoms and alter the sensitivity of a patient to the offending substance.12 Clinical ecologists report that unrecognized immune system dysregulation develops over a long period after cumulative exposure to certain chemicals. Further, overt manifestations are purported to be triggered by a single serious viral infection, major stress, or fungal infection (particularly C albicans). One currently popular hypothesis suggests that damage to T cells by chemicals or other agents causes inversion of the normal helper/suppressor T-cell ratio, and as a result alters antibody production by B cells. 10 To assess immune dysfunction, some investigators have reported that analysis of T- and B-cell surface markers and assay of a variety of specific antibodies (eg, formaldehyde and isocyanates) could be useful in diagnostic testing.10

THERAPEUTIC APPROACHES

Avoidance is a major aspect of therapy; patients are often told to ingest a defined or restricted diet or use a rotation diet, to move to another location, to create an environmentally "safe" room in their home, or in severe cases to be placed temporarily in special environmental isolation units (such units are used primarily for investigational purposes and are rarely used for treatment).

A major technique used by many practitioners of clinical ecology is sublingual or intradermal provocation-neutraliza-tion. It is used for diagnostic purposes (provocation) or for therapy to relieve symptoms (neutralization). With this procedure, a diluted extract of the suspected antigen is administered sublingually or intradermally. The prompt development of symptoms confirms the substance as causative. Once the dose that elicits symptoms has been determined, decreasing doses of the antigen are administered until symptoms disappear; this is the neutralization dose.14 20 The mechanisms for these effects are unknown. Although a large number of uncontrolled studies have been conducted and a large body of anecdotal evidence is available, no well-controlled studies have demonstrated either diagnostic or therapeutic value for provo-

Members of the Council on Scientific Affairs include the following: Yank D. Coble, Jr, MD, Jacksonville, Fla, Vice-Chairman; E. Harvey Estes, Jr, MD, Durham, NC, Chairman; C. Alvin Head, MD, Tucker, Ga, Resident Representative; Mitchell S. Karlan, MD, Beverly Hills, Calif; William R. Kennedy, MD, Minneapolis, Minn; Patricia Joy Numann, MD, Syracuse, NY; William C. Scott, MD, Tucson, Ariz; W. Douglas Skelton, MD, Macon, Ga; Richard M. Steinhilber, MD, Cleveland, Ohio; Jack P. Strong, MD, New Orleans, La; Christine C. Toevs, Greenville, NC, Medical Student Representative; Henry N. Wagner, Jr, MD, Baltimore, Md; Jerod M. Loeb, PhD, Chicago, Ill, Secretary; Robert C. Rinaldi, PhD, Chicago, III, Assistant Secretary; Steven J. Smith, PhD, Chicago, III, staff author.

This report was presented to the House of Delegates as Report K of the Council on Scientific Affairs at the American Medical Association's Interim Meeting, December 1991. The recommendation was adopted as amended in lieu of Substitute Resolution 6 (I-90) and the remainder of the report was filed. This report is not intended to be construed or to serve

as a standard of medical care. Standards of medical care are determined on the basis of all the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and tech-nology advance and patterns of practice evolve. This report reflects the views of scientific literature as of De-

cember 1991.

Reprint requests to the Council on Scientific Affairs, American Medical Association, 515 N State St, Chicago, IL 60610 (Jerod M. Loeb, PhD).

From the Council on Scientific Affairs, American Medical Association, Chicago, III.

cation-neutralization.^{1-3,6} In one recent double-blind trial of provocation-neutralization, placebo was as effective as injection of food extracts to induce either symptoms or neutralization.²¹ In contrast, two other studical ported the value of these techniqual or diagnosis and treatment.^{22,23} These three studies and other reports¹⁴⁻²⁰ have been criticized for design and methodologic flaws.

Two models have been reported that might permit controlled studies of provocation-neutralization.²⁴⁻²⁻

CANDIDA HYPERSENSITIVITY SYNDROME

Many clinical ecologists believe that the fungus C albicans is a major cause of symptoms associated with MCSS.725 It is claimed that repeated use of antibiotics, birth control pills, corticosteroids, and/or an improper or defective diet can lead to overgrowth and a systemic infection by this organism. Clinical ecologists also claim that Calbicans produces a toxin or other substances that disrupt bowel chemistry and immune function in susceptible patients. However, Candida is a constituent of the normal gastrointestinal tract in many healthy individuals. Because reliable tests to detect Candida or its putative toxin systemically in levels postulated to exist by clinical ecologists are unavailable, diagnosis is by exclusion and the only proof of Candida-related disease is response to therapy. Although considerable anecdotal evidence supports the existence of Candida hypersensitivity syndrome through its response to therapy with antifungal agents, nutritional supplements, and dietary manipulation, scientific proof from well-controlled studies has not been provided.30-3

CHRONIC FATIGUE SYNDROME

Considerable controversy exists over whether this alleged syndrome is a specific disease entity. Patients diagnosed as having CFS suffer from a disabling weakness and exhaustion that may continue for months or even years. Some patients lose the ability to think clearly, to concentrate, and to retain memory; confusion, depression, insomnia, and/or hypersomnia often are present. Flu-like symptoms also may be present and include sore throat, headache, fever, and muscle/joint pain. Diagnostic criteria for this syndrome have been proposed.35 However, no definitive laboratory tests exist. No single cause for this syndrome appears likely.8,11,36-38

An infectious or immunological mechanism has been investigated with few tangible results. In particular, suggestions have been made that infection (eg, Epstein-Barr virus, human herpesvirus

6, human T-cell leukemia virus II [HTLV-II], or other environmental insults [eg, chemicals]) may stimulate cells involved in the immune response and trigger cytokines such as interferon or interleukin 2 as well as other endogenous inflammatory mediators. In a well-controlled study, evidence was presented for the presence of serum antibodies to HTLV-II, a retrovirus, by Western blot in patients with CFS. 30 This finding awaits confirmation by other laboratories. Another well-controlled study demonstrates activation of cytotoxic CD8 cells in up to 50% of patients with CFS. 40

More than two thirds of patients with CFS appear to have an associated psychiatric disorder. 11,38 Management is difficult although depression and other psychiatric disorders may be treated with drugs and/or psychotherapy. Other treatment is symptomatic and generally not helpful. 11,38

SICK-BUILDING SYNDROME

Air quality is poor in many newly constructed buildings, and low levels of toxic agents, allergens, chemicals, or contamination with microorganisms circulating in a closed environment can produce a building-related illness for which a causative agent can be identified (eg, legionnaires' disease, humidifier fever, hypersensitivity pneumonia, and building-related asthma). In contrast to building-related illness, no specific causative agent has been identified for the symptoms occurring in patients with the sick-building syndrome. 41.42 Symptoms reported in patients with the sick-building syndrome include chest tightness, fatigue, headache, malaise, and cough, as well as eye and mucus membrane irritation. The MCSS should not be confused with the sick-building syndrome.

The lack of agreement by workers in this field over the definition of the sick-building syndrome and inclusion and exclusion criteria for patients suspected of having this syndrome has hampered efforts to design well-controlled studies. Evidence that this syndrome exists as a separate disease entity is weak. Some have claimed that mass hysteria and other psychosocial factors are responsible for symptoms. A few reports discuss building-related illness and the sick-building syndrome and provide a basis for studying the latter. 42.43

ASSESSMENT OF CLINICAL ECOLOGY

Validation of MCSS is complicated by the number and variety of symptoms and the lack of objective signs, and by the overlapping of symptoms in a number of alleged clinical ecological illnesses (eg, *Candida* hypersensitivity

and CFS) with those of recognized disorders (eg, depression and polymyalgia rheumatica). The proposed immune imbalance associated with MCSS has not been identified. No evidence based on well-controlled clinical trials is available that supports a cause-and-effect relationship between exposure to very low levels of substances and the myriad symptoms purported by clinical ecologists to result from such exposure. Several articles and books are available that seek to provide a scientific basis for such an association. 7,10,44 Such publications, while thought-provoking and interesting, fail to provide proof based on wellcontrolled clinical studies.

The view that some patients are allergic to or intolerant of environmental substances is not in itself controversial. Rarely, some individuals are known to be hypersensitive to minute concentrations of a food, drug, or inhalant allergen causing objective illness; on the other hand, clinical ecologists claim that such occurrences are common and not rare and that manifestations are subjective only. Controversy revolves around the minimum concentration of the offending substance that causes adverse reactions, the nature of such adverse effects, and the mechanisms involved.

Although malingering or hypochondriasis may be responsible for symptoms, such a cause appears unlikely in most patients. A number of clinicians have reported that the majority of patients have a definite psychosomatic disorder that could be responsible for symptoms. 32,45-49

The fact that the diagnostic tests and therapy recommended by clinical ecologists are largely unproven by controlled clinical studies does not necessarily establish the lack of scientific validity. Well-controlled studies could validate and provide a scientific basis for many of the tests and therapies associated with multiple chemical sensitivity. Attempts to design and carry out such controlled studies have been discussed at a recent 2-day National Academy of Sciences workshop, a Canadian environmental workshop, in a recent book, and in review articles. 9,10,50,51

CONCLUSIONS

Some patients present to physicians with symptoms that cannot be attributed to any known condition, disorder, or disease. Further, they may have no physical findings or laboratory abnormalities to support a standard diagnosis. The constellation of symptoms presented (eg, depression, fatigue, irritability, difficulty in breathing, headache, gastrointestinal distress, and food intolerance) resemble those seen in many illnesses. Physicians who practice

clinical ecology associate these symptoms with repeated exposure of susceptible individuals to very low levels of substances that exist in the environment or are ingested as food or liquids. After these substances have accumulated to a threshold concentration in the body, they are purported to produce immune dysfunction and result in a generalized clinical disorder-MCSS. Subsets of this syndrome include Candida hypersensitivity syndrome and CFS. Some patients diagnosed as having MCSS have an associated psychiatric disorder that could be responsible for many of the symptoms. Other patients are presumed to have a physical basis for symptoms that result from an unrecognized or undefined organic disorder.

Two medical societies have issued position papers and one has issued an in-

- 1. American Academy of Allergy and Immunology. American Academy of Allergy and Immunology position statement: clinical ecology. J Allergy Clin Immunol. 1986:78:269-271.
- 2. Task Force on Clinical Ecology, California Medical Association Scientific Board. Clinical ecology: a critical appraisal. West J Med. 1986;144:239-245.

 3. American College of Physicians. American Col-
- 3. American College of Physicians. American College of Physicians position statement: clinical ecology. Ann Intern Med. 1989;111:168-178.

 4. Randolph TG, Moss RW. An Alternative Approach to Allergies: The New Field of Clinical Ecology Unravels the Environmental Causes of Mental and Physical Ills. New York, NY: Lippincott and Cromwell: 1980
- 5. Levin AS, Byers VS. Environmental illne disorder of immune regulation. Occup Med. 1987;
- 6. Black DW. Rathe A. Total environmental allergy: 20th century disease or deception? Resident Staff Physician. 1990;36:47-54.
- 7. Crook WG. The Yeast Connection. 3rd ed. Jackson, Tenn: Professional Books; 1989.
- 8. Salvaggio JE. Clinical and immunologic approach to patients with alleged environmental injury. Ann Allergy. 1991;66:493-503.
- 9. Hileman B. Multiple chemical sensitivity. Chem
- Eng News. July 1991;69:26-42.
 10. Ashford NA, Miller CS. Chemical Exposures: Low Levels and High Stakes. New York, NY: Van Nostrand Reinhold Co; 1991.
- 11. Kroenke K. Chronic fatigue syndrome: is it real? Postgrad Med. 1991;89:44-55.
- 12. Bell IR. Clinical ecology. In: A New Medical Approach to Environmental Illness. Bolinas, Calif:
- Common Knowledge Press; 1982. 13. Rea NJ, Bell JR, Suits CW, Smiley RE. Food and chemical susceptibility after environmental chemical overexposure: case histories. Ann Aller-
- chemical overexposure: case histories. Ann Altergy. 1978;41:101-109.

 14. Council on Scientific Affairs, American Medical Association. In vivo diagnostic testing and immunotherapy for allergy: report I, part II, of the allergy panel. JAMA. 1987;258:1505-1508.

 15. Lee CH. A new test for diagnosis and treatment of food allergies. Med Bull. 1961;25:9-12.
- 16. Lee CH, Williams RI, Binkley EL. Provocative
- inhalant testing and treatment. Arch Otolaryngol Head Neck Surg. 1969;90:173-177. 17. Rinkel HJ, Lee CH, Brown DW, Willougby JW, Williams JM. The diagnosis of food allergy. Arch Otolaryngol Head Neck Surg. 1964;79:71-80. 18. Willoughby JW. Provocative food test technique.
- Ann Allergy. 1965;23:543-554.

 19. Missal SC. Food allergy in eye, ear, nose and throat disease. Otolaryngol Clin North Am. 1971;

formational report on clinical ecology.1-3 The position papers reported that no scientific evidence supports the contention that MCSS is a significant cause of disease or that the diagnostic tests and the treatments used have any therapeutic value.^{1,3} Until such accurate, reproducible, and well-controlled studies are available, the American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognized clinical syndrome.

Based on the reports in the peer-reviewed scientific literature, the Council on Scientific Affairs finds that at this time (1) there are no well-controlled studies establishing a clear mechanism or cause for MCSS; and (2) there are no well-controlled studies providing confirmation of the efficacy of the diagnos-

20. Miller JB. Food Allergy: Provocative Testing and Injection Therapy. Springfield, Ill: Charles C Thomas Publishers Inc; 1982.

21. Jewett DL, Fein G, Greenberg MH. A doubleblind study of symptom provocation to determine food sensitivity. N Engl J Med. 1989;323:429-433. 22. King WP, Rubin WA, Fadal RG, et al. Provocation-neutralization: a two-part study, part I: the intracutaneous provocative food test: a multi-center comparison study. Otolaryngol Head Neck Surg. 1988;99:263-269.

1988;99:263-269.
23. King WP, Fadal RG, Ward WA, et al. Provocation-neutralization: a two-part study, part II: subcutaneous neutralization therapy: a multicenter study. Otolaryngol Head Neck Surg. 1988;99:272-

24. Boris M, Schiff M, Weindorf S, et al. Broncho provocation blocked by neutralization therapy. J Allergy Clin Immunol. 1983;71:92. Abstract.

25. Boris M, Weindorf S, Corriel RN, Inselman LS, 25. Boris M, Weindori S, Corriei KN, Inselman LS, Schiff M. Antigen induced asthma attenuated by neutralization therapy. Clin Ecology. 1985;3:59-62.

26. Schiff M, Boris M, Weindorf S. Injection of low dose antigen attenuates the response to subsequent bronchoprovocative challenge with the same anti-gen. Am Rev Respir Dis. 1985;131(suppl, pt 2):A38.

27. Boris M, Schiff M, Weindorf S. Injection of low dose antigen attenuates the response to subsequent bronchoprovocative challenge. Otolaryngol Head Neck Surg. 1988;98:539-545.

28. Scadding GK, Brostoff J. Low dose sublingual

28. Scanding GR, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. 1986;16:483-491.
29. Truss CO. The Missing Diagnosis. 2nd ed. Birmingham, Ala: CO Truss; 1986.
30. Renfro L, Feder HM Jr, Lane TJ, Manu P, Matthews DA. Yeast connection among 100 patients with chronic fatigue. Am J Med. 1989;86: 165-169. 165-168.

31. Dismukes WE, Wade JS, Lee JY, Dockery BK, Hain JD. A randomized, double-blind trial of nystatin therapy for the candidiasis hypersensitivity syndrome. N Engl J Med. 1990;323:171-1723. 32. Black DW, Rathe A, Goldstein RB. Environmental illness: a controlled study of 26 subjects with '20th century disease.' JAMA. 1990;264:3166-3170.

33. Bennett JE. Searching for the yeast connection. N Engl J Med. 1990;323:1766-1767.

34. American Academy of Allergy and Immunology. American Academy of Allergy and Immunology position statement: candidiasis hypersensitivity syndrome. J Allergy Clin Immunol. 1986;78: tic and therapeutic modalities relied on by those who practice clinical ecology.

RECOMMENDATIONS

The Council on Scientific Affairs recognizes that the above findings are those existing at one point in time, and welcomes the opportunity to review wellcontrolled studies as they become available. It recommends the following:

- 1. That the American Medical Association continue to monitor the published literature on clinical ecology and report on it as appropriate.
- 2. That those who support a new test, procedure, or treatment must prove by appropriately controlled peer-reviewed trials that it is effective for the purposes for which it is used and that the burden should not be shifted to opponents to prove that a new test or therapy is invalid.
- 35. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108:387-389.

 36. Swartz MN. The chronic fatigue syndrome: one
- entity or many? N Engl J Med. 1988;319:1726-1728. 37. Gold D, Bowden R, Sixbey J, et al. Chronic fatigue: a prospective clinical and virologic study. *JAMA*. 1990;264:48-53.
- 38. Shafran SD. The chronic fatigue syndrome. Am J Med. 1991;90:730-739.
- 39. DeFreitas E, Hilliard B, Cheney PR, et al. Retroviral sequences related to human T-lymphotrophic virus type II in patients with chronic fatigue immune dysfunction syndrome. Proc Natl Acad Sci U.S.A. 1991:88:2922-2926.
- 40. Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. Lancet. 1991;338:
- 41. Bardana EJ Jr, Montanaro A, O'Hollaren MT. Building-related illness. Clin Rev Allergy. 1988;6:
- 42. Bardana EJ Jr. Building-related illness. In: Bardana EJ Jr, Montanaro A, O'Hollaren HT, eds. Oc-cupational Asthma. Philadelphia, Pa: Hanley and Belfus: 1991:1-18.
- 43. Hodgson MJ, Frohliger J, Permar E, et al. Symp toms and microenvironmental measures in nonprob-lem buildings. J Occup Med. 1991;33:527-533.
- 44. Cullen MR. The worker with multiple chemical sensitivities: an overview. Occup Med. 1989;2: 655-661.
- 45. Stewart DE, Raskin J. Psychiatric assessment of patients with "20th century disease" ("total allergy syndrome"). Can Med Assoc J. 1985;133: 1001-1006
- 46. Terr AI. Environmental illness: a clinical review of 50 cases. Arch Intern Med. 1986;146:
- 47. Terr AI. Multiple chemical sensitivities immunologic critique: clinical ecology theories and practice. Occup Med. 1987;2:683-694.
- 48. Brodsky CM. Allergic to everything: a medical subculture. *Psychosomatics*. 1983;24:731-742.
- 49. Pearson DJ, Rix KJB, Bentley SJ. Food allergy: how much in the mind? a clinical and psychiatric study of suspected food hypersensitivity. *Lancet*. 1983;1:1259-1261.
- 50. Hileman B. Chemical sensitivity: experts agre on research protocol. Chem Eng News. April 1991; 69:4-5.
- 51. Davies JW, Wilkins K, eds. Proceedings of the Environmental Sensitivities Workshop. *Chronic Dis* Canada. January 1991.

In Reply.—We thank Drs Alagona, Cooley, and Varipapa for their interest in our research. Their letters do not directly address the design or findings of our study—that depending on the patient's clinical presentation, self-referral for diagnostic imaging examinations in office practice results in 1.7 to 7.7 times higher utilization and 1.6 to 6.2 times higher costs than when physicians refer their patients to radiologists. Rather, they present, in anecdotal fashion, their perceptions about some related issues, specifically patient convenience, the relative quality of imaging by radiologists and self-referring physicians, and radiologists' suggesting follow-up studies.

As Alagona notes, it is more convenient for patients to receive imaging examinations in the offices of their physicians. However, implicit in Alagona's statement is that "convenience" may importantly contribute to the observed higher utilization by promoting the performance of marginal examinations that otherwise might not be performed. The policy issue raised by our research is whether the associated higher costs are sufficiently justified by improved care and patient outcomes. There is nothing in the literature to suggest that these higher levels of utilization consequently benefit patients.

We are unaware of any studies to support Cooley's and Alagona's claim that imaging by nonradiologist physicians is superior to imaging performed by radiologists. Most of what limited research is available addresses the quality of images and indicates superior performance attributable to radiologists. A blinded study by Pennsylvania Blue Shield (written communication, 1985) found that radiologists' chest roentgenograms were of diagnostic quality in 94% of cases; 41% or more of chest roentgenograms performed by all other specialties were not sufficient for diagnostic purposes. Radiologists' and orthopedists' musculoskeletal films were judged to be of similar quality (87% acceptable). Hopper et al¹ supported this result and radiologists were also superior in the accuracy of their interpretations. Certainly, with 4 to 7 years of formal training, depending on subspecialization, radiologists receive far more extensive education than other specialists in the physical basis of imaging, quality control, and image interpretation.

What Varipapa calls "auto-referral" represents the common situation of a physician "ordering" additional services within his or her primary specialty interest—a different phenomenon than we investigated, but also a significant concern with respect to high rates of utilization for all specialties. Unlike most specia les, however, radiologists generally require the consent of a referring physician before they may perform and be compensated for additional studies. This represents a level of oversight that does not exist for most other specialties. We are unaware of studies that quantitate the utilization or cost effects of "auto-referral" for radiology or any other specialty but agree with Varipapa that this would be an important focus for future research.

We appreciate the opportunity afforded us by the letters of Varipapa, Cooley, and Alagona to expand on issues affecting physician practices. As we have noted, the subjects of their letters were not those we addressed in our research. Nonetheless, we agree that they are important related concerns that deserve investigative attention.

> Bruce J. Hillman, MD University of Virginia School of Medicine Charlottesville, Va George T. Olson, MRP Patricia E. Griffith, MPhil William R. Nelson, MA Alta Health Strategies, Inc Los Angeles, Calif

Jonathan H. Sunshine, PhD American College of Radiology Reston, Va Catherine A. Joseph Stephen D. Kennedy, PhD ABT Associates Cambridge, Mass Lee B. Bernhardt United Mine Workers of America Health and Retirement Funds Washington, DC

1. Hopper KD, Rosetti GF, Edmiston RB, et al. Diagnostic radiology per a method inclusive of all interpreters of radiographic examinations respecialty. Radiology. 1991;180:557-561.

Unrecognized False-Positive Ketones From Drugs Containing Free-Sulfhydryl Group(s)

To the Editor.—There are a growing number of drugs that are present in the blood and/or excreted in the urine as free-sulfhydryl compounds. This list includes established drugs like dimercaprol (British antilewisite, BAL), penicillamine, cysteine, and acetylcysteine, plus newer drugs like mesna (or dimesna) and captopril. In alkaline medium, free-sulfhydryl compounds react with a purple color similar to that of ketone bodies (acetoacetic acid and acetone but not β-hydroxyhutyric acid) in the nitroprusside test. Since the nitroprus test is used currently in all commercial dipsticks and in Acetest tablet assay (Ames) for the detection of ketone bodies in urine and blood (serum), the positive interference with free-sulfhydryl compounds is of great importance, particularly in diabetics² and in those with suspected hepatocellular injury (eg, acetaminophen poisoning³ and chemotherapy).¹ Documented cases of patients who received or almost received inappropriate therapy with insulin due to spurious ketonuria or ketonemia already exist.³⁴ Although the interference with free-sulfhydryl compounds for ketone testing has been well established in the literature, recent proficiency testing results of the College of American Pathologists indicate that over 97% of the (more than 6000) clinical laboratories in the United States regularly fail to recognize these false-positive ketone reactions in the urine. Thus, until laboratory performance improves (there are reported techniques for the recognition or elimination of interference or more specific tests (eg, KetoSite™ ketone test card for the enzymatic detection of β-hydroxybutyrate in the blood) are widely available, increased awareness of clinicians is critical to avoid possible untoward interventions based on a false-positive laboratory test for ketones in patients receiving these drugs.

Gyorgy Csako, MD Ronald J. Elin, MD, PhD National Institutes of Health Bethesda, Md

1. Csako G. False-positive results for ketone with the drug mesna and other free sulfhydryl compounds. Clin Chem. 1987;33:289-292.

2. Graham P, Naidoo D. False-positive Ketostix in a diabetic on antihypertensive therapy. Clin Chem. 1987;33:1490.

3. Williamson J, Davidson DF, Boag DE. Contamination of a specimen with N-acetylcysteine infusion: a cause of spurious ketonemia and hyperglycaemia. Ann Clin Biochem. 1989;26:207-208.

4. Viar MJ, Wright RK. Spurious ketonuria after mesna therapy. Clin Chem. 1987; 33:913.

5. Poon R, Hinberg I. One-step elimination of interference of free-sulflydry-containing drugs with Chemstrip ketone readings. Clin Chem. 1990;36:1527-1528.

Clinical Ecology

To the Editor.—The recent Council Report¹ on clinical ecology repeats a mistake that has been made in position papers published by other medical societies. The report confuses criticism of a mode of medical practice (clinical ecology) with analysis of

several clinical conditions. Does the Council on Scientific Affairs really mean to imply that chronic fatigue syndrome (CFS), sick building syndrome (SBS), and multiple chemical sensitivity syndrome (MCSS) are inventions of clinical ecology? Each of these syndromes is the target of serious research by a broad spectrum of medical and environmental scientists.

Well-conducted surveys have suggested that more than 20% of office workers suffer from nonspecific, building-related complaints.2 The World Health Organization made one of the first attempts to group these symptoms into one general definition of SBS.3 Extensive research on the health effects of indoor air pollution has failed to identify a specific causative agent for SBS. Nonetheless, the irritant symptoms included in the syndrome have been reproduced in controlled settings when individuals are exposed to a mixture of agents found in problem buildings. 4 Epidemiology has also identified environmental, as well as psychosocial factors associated with SBS complaints.^{5,6} Specific environmental interventions can reduce the incidence of SBS complaints in a building population and "cure" the syndrome in individuals. Though our understanding of the health effects of low-level air pollutants is hardly complete and definitional problems of SBS remain, several federal agencies and professional organizations have responded to SBS as if it were a very real problem. I cannot understand why the Council has chosen to discuss SBS in a report titled "Clinical Ecology," and to do so only briefly and dismissively.

I am most concerned about the tone of the Council Report. Though scientific evidence is not adequate to label CFS, SBS, and MCSS as new, distinct diseases, people with these complaints are truly suffering and often debilitated in the prime of their life. The Council may disparage clinical ecologists' efforts to help these people, but someone must attend to their very pressing needs. It is just such dismissal that leads these

people to other more sympathetic healers.

Many of the Council's comments about nonspecific, subjective syndromes could be applied to chronic pain conditions for which medical therapy has been equally nihilistic until very recently. Principles of functional restoration, behavioral therapies, and other strategies learned in the care of people with chronic pain provide a rational paradigm for treatment of several syndromes discussed in the Council Report. Functional restoration shifts the focus of physician and patient alike away from discussions of pain and debates about mind and body to improving physical and social functioning.

As physicians we must not forget our duty to assuage suffering. As scientists we must aggressively pursue an understanding of unexplained patterns of health complaints especially when they challenge our present models of pathophysiology.

> Robert K. McLellan, MD, MPH Exeter (NH) Hospital

Council on Scientific Affairs, American Medical Association. Clinical ecology.

JAMA. 1992;268:3465-3467.

2. Kreiss K. The sick building syndrome: where is the epidemiologic basis. Am J Public Health. 1990;80:1172-1173.

3. Molhave L. Controlled experiments for studies of the sick building syndrome. Ann N Y Acad Sci. 1992;641:46-55.

4. Otto DA. Assessment of neurobehavioral response in humans to low-level volatile organic compound sources. Ann N Y Acad Sci. 1992;641:248-260.

5. Mendell NJ, Smith AH. Consistent pattern of elevated symptoms in airconditioned office buildings: a reanalysis of epidemiologic studies. Am J Public Health. 1990;80:1193-1198.

6. Norback D, Torgen M, Edling C. Volatile organic compounds, respirable dust, and personal factors related to prevalence and incidence of sick building syndrome in primary schools. Br J Ind Med. 1990;47:733-741.

In Reply.—The American Medical Association Council on Scientific Affairs agrees with Dr McLellan that many patients with symptoms and a medical history suggestive of a multiple chemical sensitivity (MCS)-related syndrome are not helped by traditional medicine. We dispute his assertion that the clinical ecology report is insensitive to the suffering of patients with CFS, SBS, or any other MCS-related illnesses. The large body of anecdotal evidence supporting the validity of various hypotheses as the cause of MCS-related syndromes, or the value of suggested therapies, is impressive. However, the history of medicine is filled with numerous examples in which anecdotal evidence was widely accepted as proof of hypotheses for the cause of disease or as support for the value of therapies for a specific disease; when it became possible to carry out controlled studies, the validity of these hypotheses or therapies could not be demonstrated.

The Council on Scientific Affairs believes that it is unwise to subject patients to unproved therapies for unproved disorders. That some patients with MCS-related syndromes are helped by clinical ecology practitioners probably results because psychosomatic or psychopathologic mechanisms are primary causes of symptoms; these patients also have confidence that these physicians can help them.

McLellan's assertion that the report is totally negative is incorrect. The clinical ecology report states that an organic basis may exist for MCS-related symptoms in some patients. The report also discusses (with references) significant attempts that are being made to study these syndromes using scientifically accepted methods.

With regard to the issue of SBS, once a substance or substances have been identified as the source of symptoms (as the report states), it can be labeled a building-related illness. As is the case for all MCS-related syndromes, the heterogeneity of the SBS makes it difficult to define it or to develop methods to study it.

Evidence may be developed in the future that supports the validity of some aspects of clinical ecology. However, contrary to the position of practitioners of clinical ecology, the Council on Scientific Affairs believes that no credible evidence exists at the present time that permits acceptance of the existence of MCS-related disorders or demonstrates the validity of treatments used by clinical ecology practitioners.

> Steven J. Smith, PhD Jerod M. Loeb, PhD Council on Scientific Affairs American Medical Association Chicago, Ill

Treating Cancer With Coffee Enemas and Diet

To the Editor.—It is crucial that we, as physician-scientists, remain objective especially when dealing with matters that are as emotive as the diet and cancer issue. The Special Communication entitled "A Critique of the Rationale for Cancer Treatment With Coffee Enemas and Diet" carries a proselytizing tone against this therapy, as much as those who proselytize for the therapy. Can't we in the medical profession rise above this type of subjectivity?

The author identified only those aspects of the Gerson therapy that cannot be supported by current scientific knowledge. He conspicuously omits references to the Gerson therapy's emphasis on fresh fruits and vegetables as a highquality vitamin source, which has been strongly suggested to be of potential benefit in recent medical literature. He does not comment on the proposed long-term effects of our contemporary sodium-rich, potassium-poor diet on cellular function, the reversal of which formed a large part of Max Gerson's rationale. Is there any evidence to support or discount the idea that artificial substances are eliminated via the colon as an important part of our excretory physiology? If so, are there ways to enhance this, and can we test Gerson's unusual approach to see if it does enhance such an effect?

Some of the rationales that were given in the Gerson material are incorrect; however, we must not forget that much

ENVIRONMENT !. AND OCCUPATIONAL HEALTH SCIENCES INSTITUTE

681 Frelingh: en Road ■ P.O. Box 1179 ■ Piscataway, N.J. 08855-1179 **■** (908) 932-0190 **■** Fax (908) 932-0127

Occupational Health Division (908) 932-0182 (908) 932-0130 FAX

January 22, 1993

Editor Jama 515 N. State Street Chicago, IL 60610

RE:

Council on Scientific Affairs Statement

To the Editor:

We were disappointed to read the Council on Scientific Affairs Statement on Clinical Ecology We are not advocates of Clinical Ecology nor of the non-scientific approaches exemplified by many of its practitioners, but your statement is an egregious example of throwing out the baby with the bathwater: what about the patients? Many of us who are not Clinical Ecologists, but rather traditionally trained and certified Occupational Medicine Physicians with expertise in chemical-induced illness, have been seeing some of the various groups of patients identified in the Statement over a number of years. We are not certain of the nature of their disorders, but we find many of their symptoms compelling enough to warrant careful scientific investigation. In this vein we have successfully competed for NIH sponsored research. We are engaged in a broad program of investigation to better understand the nature of these disorders, which clearly exist independent of direct influences from ecologists or other non-standard practitioners.

Clinical Ecologists are a relatively easy target, whereas what is wrong with the patients you discuss is a real problem. Whether or not it is new onset, many have significant disability which does contribute significantly to the cost of their he a care. Complex syndromes require careful, thorough, and sensitive investigation. The text and title of your position paper suggests that in addition to its being out of date (proceedings of two national meetings on chemical sensitivities organized by The National Research Council and the Agency for Toxic Substances and Disease Registry^{1,2} have been published since it was written). it is lacking in desired scientific thoroughness and patientcentered ampassion because it is the patients, often irrespective of the practitioners, who believe that exposures are producing their symptoms.

We believe that in addition to the Council's two recommendations on Clinical Ecology per se, that a third should endorse and support the careful scientific investigation of perplexing clinical syndromes including Multiple Chemical Sensitivity Syndrome and Sick Building Syndrome.

Sincerely,

Howard M. Kipen, MD, MPH Associate Professor and

Medical Director

Nancy Fiedler, PhD Assistant Professor

HMK/NF:pahjamadit.ltr

References:

- 1. <u>Multiple Chemical Sensitivities</u> (Addendum to Biologic Markers In Immunotoxicology). National Research Council. Washington, DC. National Academy Press, 1992.
- 2. Proceedings of the Association of Occupational and Environmental Clinics (AOEC) Workshop on Multiple Chemical Sensitivities. Toxicology & Industrial Health, Vol. 8, No. 4, July-August 1992.

NEWS AND ANALYSIS

AMA Group Wants More Data on Multiple Chemical Sensitivity

The American Medical Association (AMA) says that evidence is still insufficient to classify multiple chemical sensitivity (MCS) as a recognized clinical syndrome, but stopped short of saying that the syndrome definitely does not exist.

In the December 23-30, 1992, issue of *The Journal of the American Medical Association (JAMA)*, the AMA's Council on Scientific Affairs recommended that the association continue to monitor published literature and called for MCS advocates to provide appropriately controlled, peer-reviewed trials.

In the JAMA article, which was originally presented in 1991, the council reviews previous discussion relating to the field of clinical ecology—medical practitioners who diagnose and treat conditions resulting from environmental causes—as well as MCS.

These advocates say that once individuals develop this sensitivity, they react to other challenges by environmental agents, resulting in allergy-like symptoms, food and chemical

intolerance, rhinitis, difficulty breathing, and a variety of other manifestations.

Mary Lamielle, president of the National Center for Environmental Health Strategies (NCEHS), a group that tracks MCS topics, took issue with the JAMA report, telling IAQU that it is unfortunate the AMA council used what she termed "narrow and dated" information. She referred to studies that have come out since the 1991 meeting at which the AMA report was first presented. She referred specifically to a National Academy of Sciences report on MCS that was published in 1992. That report consisted of papers presented as a result of a National Research Council workshop on MCS. The papers in the report were not peer reviewed.

Lamielle also charged that the AMA was purposely confusing two issues — clinical ecology and MCS — in an attempt to establish what she said was "guilt by association."

January 1993

Indoor Air Quality Update

13

Roadblocks in Research

The council found several stumbling blocks for those who contend that such a syndrome as MCS exists. Citing the number and variety of symptoms, a lack of objective signs, and the overlapping of MCS symptoms with recognized disease symptoms, the council concluded that it is currently unable to validate claims of MCS.

However, the group did seem to rule out large-scale hypochondria. The report concludes: "Although malingering or hypochondriasis may be responsible for symptoms, such a cause appears unlikely in most patients." However, the council did say that many patients have definite psychosomatic disorders that could be responsible.

While saying that there is no evidence solidly in favor of MCS, the JAMA article was careful to

point out that this deficiency does not entail a lack of scientific validity.

The AMA council did recognize that some patients "present to physicians with symptoms that cannot be attributed to any known condition, disorder, or disease. Further, they may have no physical findings or laboratory abnormalities to support a standard diagnosis."

For more information on the JAMA article, contact: The American Medical Association, Council on Scientific Affairs, 515 N. State Street, Chicago, IL 60610, USA.

For more information on MCS, contact: Mary Lamielle, National Center for Environmental Health Strategies, 100 Rural Avenue, Voorhees, NJ 08043, USA; (609) 429-5358.